

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 February 2000 (11.02.00)	
International application No. PCT/EP99/04286	Applicant's or agent's file reference 0098249-vers
International filing date (day/month/year) 21 June 1999 (21.06.99)	Priority date (day/month/year) 25 June 1998 (25.06.98)
Applicant RASPE, Eric et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:29 December 1999 (29.12.99)☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer F. Baechler Telephone No.: (41-22) 338.83.38
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 0098249-vers	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/04286	International filing date (day/month/year) 21/06/1999	Priority date (day/month/year) 25/06/1998
International Patent Classification (IPC) or national classification and IPC G01N33/50		
Applicant MERCK PATENT GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 29/12/1999	Date of completion of this report 09.08.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bradbrook, D Telephone No. +49 89 2399 7413 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/04286

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-40 as originally filed

Claims, No.:

1-9 as originally filed

Drawings, sheets:

1/13-13/13 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 9.

because:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/04286

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 9 are so unclear that no meaningful opinion could be formed (*specify*):
- see separate sheet**
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-8
	No: Claims
Inventive step (IS)	Yes: Claims 1-8
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-8
	No: Claims

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

s separat sh et

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/04286

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section III

1. No establishment of opinion

Claim 9 is directed to "Use of a screening process ... for the characterization, justification and claim of the mechanism of action of ...". The scope of this claim is considered to be unclear to the extent that no meaningful opinion can be given. In particular, the terms "justification" and "claim" are unclear in their present context. One interpretation is that the claim attempts to seek some sort of protection for the mechanism of action of the substances of interest: such subject-matter would fall under the provision of Article 34(4)(a)(i) PCT, as defined by Rule 67.1(i) PCT, for which no opinion is required.

Section V

2. The present invention is based on the observation that the Rev-erb receptors are negative regulators of transcription of the apo C-III gene, which is associated with hypertriglyceridaemia and hyperlipidaemia. Therefore, the claims are directed to the use of said receptors and response elements thereof to screen for active substances (claims 1 and 2), processes for screening for substances which influence expression of Rev-erb and genes under its control (claims 3 and 4), and uses of active substances (claims 5-8).

3. Reference is made to the following documents:

D1: WO-A-97 12853 (Ligand Pharmaceuticals Inc.; 10.04.97);

D2: Adelmant et al., Proc.Natl.acad.Sci.USA, Vol.93, pp.3553-3558 (1996);

D3: Lavrentiadou et al., Circulation, Vol.92, p.129 (1995).

D1 describes compounds having RXR homo- or heterodimer agonist / antagonist activity (abstract).

D2 discloses that Rev-erb receptors show transcriptional repressing activity through RevRE placed in its natural context or upstream of a heterologous promotor. Thus, Rev-erb α mediates self-regulation as its promotor includes a

functional RevRE (abstract).

D3 shows modulation of the ApoC-III promotor activity by heterodimers of ligand dependent nuclear receptors RXR α -RAR α , RXR α -T3R[SPEC0803] and RXR α -PPAR α .

4. Novelty and Inventive step (Article 33(2) and (3) PCT)

No single prior art document discloses a link between Rev-erb receptors and regulation of the ApoC-III gene, or indeed any factors involved in controlling lipid metabolism. Moreover, no combination of available prior art documents would provide a specific indication for the skilled person that such a link exists. D2 discusses the binding of Rev-erb α as a monomer to an AGGTCA motif, and the possibility that Rev-erb α represses transcriptional activity by acting as a competitor for other ligand-inducible receptors for the said motif (bridging paragraph p.3557-3558). The AGGTCA motif is also the consensus sequence for retinoid X and retinoic acid receptors (RXRs and RARs respectively), dimers thereof binding to a response element comprising a direct repeat of the motif. The type of dimer which binds is according to the spacing of the repeats (D1: p.2, l.23-28). As apolipoprotein AI genes are responsive to RXR but not to RAR (D1: p.3, l.1-2), and the ApoC-III promotor is regulated by heterodimers of RXR (see D3), one might consider that Rev-erb α may be able to play a role in competing with RXR for the response elements, thereby inhibiting expression of these genes. However, such a conclusion would have been purely speculative and is made here very much ex post facto.

Therefore, the subject-matter of claims 1-8 is considered to be new and inventive.

5. The written opinion has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the following document would be relevant with respect to novelty and/or inventive step (Article 33(2) and (3) PCT):

Vu-Dac et al., Proc.Natl.Acad.Sci.USA, Vol.273, pp.25713-25720 (Oct.1998).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/04286

Section VI

6. Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO-A-98 52968	26.11.98	21.05.98	21.05.97

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above document would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT). Furthermore, should the present application be entered into the regional phase, the above document could be relevant to the question of novelty.

Section VIII

7. The following objections are under Article 6 PCT:

- a. Claims 1-4 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The specification is based on the finding that Rev-erb receptors are negative regulators of the apoC-III gene (p.3, 2nd paragraph): the examples deal specifically with regulation of apoC-III expression, and no disclosure is made to the effect that any other gene involved in lipid metabolism may be regulated in a similar way. Therefore, claims 1-4 should be restricted to the regulation of apoC-III, as there is no support for claims covering lipid metabolism in general.
- b. Claim 3 is formulated in such a way that it is difficult to determine exactly what are the essential features of the process, particularly due to the repeated use of "and/or". For instance, the presence of a Rev-erb response element within a promotor controlling transcription of a reporter gene would appear to be essential, but is not apparent from the present wording.
- c. Claim 5 is directed to "Use of a substance selected by a screening process ... for the preparation of a composition ...". This claim seeks to define the subject-matter for which protection is sought by a result to be achieved, i.e. the outcome of a screening process, rather than by the features of the substance in question. In consequence, the scope of the claim is unclear.

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 0098249-vers	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 99/ 04286	International filing date (day/month/year) 21/06/1999	(Earliest) Priority Date (day/month/year) 25/06/1998
Applicant MERCK PATENT GMBH et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

USE OF REV-ERB FAMILY OF RECEPTORS UN SCREENING

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 99/04286

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 G01N33/50 G01N33/566

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 G01N C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 98 52968 A (SALK INST FOR BIOLOGICAL STUDI) 26 November 1998 (1998-11-26) the whole document ---	1-8
Y	WO 97 12853 A (LIGAND PHARM INC) 10 April 1997 (1997-04-10) claims page 2, line 14 - line 28 ---	1-8
Y	WO 97 08550 A (SALK INST FOR BIOLOGICAL STUDI) 6 March 1997 (1997-03-06) claims page 3, line 18 - line 26 page 8, line 10 - page 9, line 26 ---	1-8
Y	WO 96 41013 A (LIGAND PHARM INC) 19 December 1996 (1996-12-19) claims ---	1-8
	-/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 November 1999

Date of mailing of the international search report

12/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Routledge, B

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 99/04286

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VU-DAC, NGOC ET AL: "The nuclear receptors peroxisome proliferator-activated receptor alpha and Rev-erbalpha mediate the species-specific regulation of apolipoprotein A-I expression by fibrates." JOURNAL OF BIOLOGICAL CHEMISTRY, (OCT. 2, 1998) VOL. 273, NO. 40, PP. 25713-25720. ISSN: 0021-9258., XP002099903 cited in the application	1-4
Y	the whole document	5-8
Y	--- ADELMANT ET AL: "A functional Rev-erbalpha responsive element located in the human Rev-erbalpha promoter mediates a repressing activity" PROC.NATL.ACAD.SCI. USA, vol. 93, April 1996 (1996-04), pages 3553-3558, XP002099904 cited in the application	1-8
Y	the whole document	
Y	--- LAVRENTIADOU ET AL: "Modulation of the ApoCIII promoter activity by heterodimers of ligand dependent nuclear receptors RXR -alpha- RAR -alpha, RXR -alpha-T3R-beta and RXR -alpha-PPAR-alpha" CIRCULATION, vol. 92, no. 8, 13 November 1995 (1995-11-13), page 129 XP002088668 the whole document	1-8
Y	--- JANUZZI ET AL: "Characterization of the mouse apolipoprotein ApoA-1/Apoc-3 gene locus: Genomic, mRNA, and protein sequences with comparisons to other species" GENOMICS, vol. 14, no. 4, December 1992 (1992-12), pages 1081-1088, XP002088670 the whole document	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/04286

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9852968 A	26-11-1998	NONE	
WO 9712853 A	10-04-1997	AU 7074296 A	09-04-1997
		AU 7362496 A	28-04-1997
		BR 9610624 A	16-03-1999
		CA 2232288 A	27-03-1997
		CA 2233888 A	10-04-1997
		EP 0859608 A	26-08-1998
		EP 0873295 A	28-10-1998
		NO 981192 A	18-05-1998
		NO 981501 A	02-06-1998
		WO 9710819 A	27-03-1997
WO 9708550 A	06-03-1997	US 5906920 A	25-05-1999
		AU 6508196 A	19-03-1997
		CA 2230637 A	06-03-1997
		EP 0907886 A	14-04-1999
WO 9641013 A	19-12-1996	AU 6263996 A	30-12-1996
		CA 2222562 A	19-12-1996
		EP 0832295 A	01-04-1998

INTERNATIONAL SEARCH REPORT

International Application No.

PC./EP 99/04286

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 G01N33/50 G01N33/566

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 G01N C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 November 1999

Date of mailing of the international search report

12/11/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Routledge, B

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 99/04286

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VU-DAC, NGOC ET AL: "The nuclear receptors peroxisome proliferator-activated receptor alpha and Rev-erbalpha mediate the species-specific regulation of apolipoprotein A-I expression by fibrates." JOURNAL OF BIOLOGICAL CHEMISTRY, (OCT. 2, 1998) VOL. 273, NO. 40, PP. 25713-25720. ISSN: 0021-9258., XP002099903 cited in the application	1-4
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Y	LAVRENTIADOU ET AL: "Modulation of the ApoCIII promoter activity by heterodimers of ligand dependent nuclear receptors RXR -alpha- RAR -alpha, RXR -alpha-T3R-beta and RXR -alpha-PPAR-alpha" CIRCULATION, vol. 92, no. 8, 13 November 1995 (1995-11-13), page 129 XP002088668 the whole document	1-8
Y	JANUZZI ET AL: "Characterization of the mouse apolipoprotein ApoA-1/Apoc-3 gene locus: Genomic, mRNA, and protein sequences with comparisons to other species" GENOMICS, vol. 14, no. 4, December 1992 (1992-12), pages 1081-1088, XP002088670 the whole document	1-8

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Information on patent family members

International Application No

PCT/EP 99/04286

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9852968	A	26-11-1998	NONE
WO 9712853	A	10-04-1997	AU 7074296 A 09-04-1997
			AU 7362496 A 28-04-1997
			BR 9610624 A 16-03-1999
			CA 2232288 A 27-03-1997
			CA 2233888 A 10-04-1997
			EP 0859608 A 26-08-1998
			EP 0873295 A 28-10-1998
			NO 981192 A 18-05-1998
			NO 981501 A 02-06-1998
			WO 9710819 A 27-03-1997
WO 9708550	A	06-03-1997	US 5906920 A 25-05-1999
			AU 6508196 A 19-03-1997
			CA 2230637 A 06-03-1997
			EP 0907886 A 14-04-1999
WO 9641013	A	19-12-1996	AU 6263996 A 30-12-1996
			CA 2222562 A 19-12-1996
			EP 0832295 A 01-04-1998